DYSFUNCTION OF THE SEBACEOUS GLANDS ASSOCIATED WITH PELLAGRA*†

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The typical dermatitis of pellagra occurs on the hands, feet, face, neck, and other exposed surfaces of the body. Many pellagrins present, in addition, an entirely different type of skin lesion involving the sebaceous glands, which occurs also on the face but appears to be independent of any effect of radiant energy. This lesion is characterized by the development of innumerable plugs of abnormal, inspissated sebum which project from the dilated orifices of the sebaceous follicles, thus giving to the surface a rough appearance which feels like shark skin or sandpaper on palpation. When the plugs are small they reflect the light and have been described in the literature as sulphur flakes (1). The larger plugs are grayish yellow in color with darker tips. The skin in this region is definitely dry because the natural oily sebum either is not being evolved or fails to reach the surface.

Wilson (1, 6) of Cairo, Egypt, tests the condition of the skin by drawing a microscope slide over the surface of the nose. He demonstrated that the "sulphur flakes" powder away and leave no greasy smear on the slide as is the case with the non-pellagrin, where the sebaceous glands are functioning normally.

The earlier lesions are not readily visible and can be detected best by palpation. They appear first about the alae nasi and

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spread over the nose, the lips, and in advanced cases, on the forehead and chin, thus involving the whole face. The lesions themselves are not inflammatory but may be present in patients who show the typical inflammatory dermatitis of pellagra on the face. The sebaceous gland lesions occur most frequently in pellagrins who have the usual dermatitis on the hands, arms and feet but not on the face, and frequently appear before the development of the characteristic dermatitis of pellagra. However, severe pellagra often occurs without these characteristic sebaceous gland lesions and there is reason to believe that they are not an essential part of the typical pellagra syndrome.

The absence of natural oily sebum suggests that the condition described above is a deficiency type of asteatosis rather than seborrhea. For convenience and brevity the term "dyssebacia" will be used subsequently to refer to the syndrome.

A second type of sebaceous gland change which gives rise to a very similar papular lesion has been reported as occurring in association with vitamin A deficiency (19–28). This lesion, phrynoderma or toadskin, rarely occurs on the face but is usually distributed over the extremities and shoulders, arising presumably from the pilosebaceous follicles, but rarely involving the sites where the sebaceous glands are most numerous.

HISTORY

A complete historical survey of the sebaceous gland lesion associated with pellagra will not be attempted. However, descriptions of this lesion appeared in the English literature as early as 1909 when Siler (2), Watson (3), and Parker (4) described it at the International Conference on Pellagra held in Columbia, S. C. and referred to the lesion as if it were well-known at that time. Pearson (5) reported it as one of the common lesions of pellagra in Egypt. Since then, there have been numerous references to it in the literature (6–18).

Our interest in the subject dates from an observation by Smith in 1932 (29) that rats, when fed a diet similar to the ones on which human beings develop pellagra, have abnormal sebaceous secretions on the tail and histologically these glands show

almost complete atrophy. In a later study in 1935 the occurrence of typical sebaceous gland lesions in pellagra patients at this hospital was recorded by Smith and Sprunt (9).

ANIMAL EXPERIMENTS

In the animal studies albino rats of the Wistar strain were used throughout. The animals were housed in experimental cages with iron grid floors for the elimination of the excreta. The experimental basic diets were fed ad lib and the supplements given individually in exact amounts. Rats were weighed weekly. In many instances a given rat served as its own control for the histological change which occurred as the result of a given supplement. A biopsy of the tail was made at the end of the depletion period at which time the supplement was given for a period of 30 days or more when a final section was made for comparison. Autoclaved yeast restored the atrophic sebaceous glands to normal in every instance.

Since our first studies in 1932 were carried out with a pellagra-producing diet of natural foodstuffs, having of course a mixed deficiency, it was logical to seek a more purified diet. That of Bourquin and Sherman (9) proved best for our purpose. Due to vitamin contamination from the natural sources of the carbohydrate (cornstarch) and of vitamin B_1 (wheat extract), most of the factors of the G-complex were supplied with the exception of riboflavin. Rats maintained on this riboflavin deficient diet developed the sebaceous gland lesions and were cured with either synthetic riboflavin or autoclaved yeast. As a further step in the purification of the basic diet, vitamin B_1 was supplied as thiamin chloride and carbohydrate as sucrose. This diet will be referred to subsequently as G-free diet #25[1] and serves as the basic diet for future comparisons, since it is lacking in all

[1] G-free diet #25:

	per cent
Casein (extracted with alcohol)	18
Sucrose	78
Butterfat	8
Cod liver oil	2
Salt mixture (Osborne and Mendel)	4

Thiamin chloride. 20 micrograms / rat / day.

the factors of the vitamin G (B_2) complex. Oddly enough, when rats were placed on this diet, but supplemented with 20 micrograms daily of synthetic riboflavin, they developed the same type and degree of sebaceous gland change as occurred on the riboflavin deficient diet of Bourquin and Sherman. If the tail were biopsied at this time and the rat fed autoclaved yeast at the level of 0.5 gm. per day, there was an immediate growth impulse, and a prompt improvement in the gross appearance of the tail followed by a complete regeneration of the damaged sebaceous glands. To the basic G-free diet #25 the following supplements were added singly and in various combinations: riboflavin, vitamin B_6, nicotinic acid, adenylic acid (muscle), autoclaved yeast and crude liver extract. The combinations and single supplements are outlined in table 1 which indicates also the effect on the sebaceous glands.

The effect of vitamin B_1 deficiency and vitamin A deficiency on the sebaceous glands was also studied (30), and it was found that when the rats consumed the G-complex portion of the diet mixed in with the basic diet, sebaceous gland lesions occurred quite as regularly and to almost as great a degree on the A deficient diet as on the G-complex deficient diet. Whereas, if the G-complex was fed separately, thus maintaining an adequate level in spite of anorexia, the animals were almost completely protected against the damage to the sebaceous glands. On the other hand, no protection resulted when vitamin A was given separately in the G-complex deficient diet. Thus we concluded that the sebaceous gland changes observed in rats occurs specifically as a result of vitamin G-complex deficiency.

As we see from the tabulated data (table 1), not one of the synthetic factors when fed singly to rats on a completely G-complex deficient diet is sufficient to protect them from developing the sebaceous gland lesion described. If riboflavin is the only deficiency in the diet, then synthetic riboflavin alone will protect, but if all other factors of the G-complex are missing from the diet, pure riboflavin has little or no effect. Nor has vitamin B_6 alone, in the absence of the other G-complex factors, any protective effect against the sebaceous gland lesion. However, the edema

TABLE 1

BASIC DIET	DEFICIENCY OF BASIC DIET	SUPPLEMENT ADDED TO BASIC DIET	NUMBER OF RATS	GROSS SYMPTOMS	SEBACEOUS GLAND CHANGE
Pellagra producing diet	Primarily N.A. and R.F.	None	17	Alopecia	+++
Bourquin-Sherman diet	R.F.	None	107	Alopecia	+++
		R.F.	4	Normal	Normal
		A.C.Y.	18	Normal	Normal
G-free diet #25	G (B_2) complex	None	33	Dermatitis	+++
		R.F.	124	Dermatitis	+++
		B_6	32	Alopecia	+++
		N.A.	8	Severe dermatitis	+++
		A.A.	2	Severe dermatitis	+++
		R.F. + N.A.	22	Severe dermatitis	+++
		B_6 + N.A.	24	Alopecia	+++
		N.A. + A.A.	2	Severe dermatitis	+++
		R.F. + N.A. + A.A.	2	Severe dermatitis	+++
		B_6 + N.A. + A.A.	2	No dermatitis	+++
		P.L.E. (L)	10	Coat greasy	+++
		B_6 + R.F.	16	No dermatitis	+ to normal
		B_6 + R.F. + N.A.	16	No dermatitis	+
		B_6 + R.F. + N.A. + A.A.	2	No dermatitis	Normal
		C.L.E. (L)	9	Normal	Normal
		A.C.Y.	114	Normal	Normal
		U.Y.	15	Normal	Normal
Stock	None		10	Normal	Normal
Vitamin A deficient diet	A	None			++
		A			Normal
Vitamin deficient diet	All vitamins	B_1, G complex, D			+ to normal

A.C.Y., autoclaved yeast; U.Y., untreated yeast; C.L.E., crude liver extract; R.F., riboflavin; N.A., nicotinic acid; A.A, adenylic acid (muscle).

observed in the vitamin B_6 deficient rat and demonstrated photomicrographically (fig. 1a) is relieved by the administration of pure synthetic vitamin B_6[2] (fig. 1b). A combination of B_6 and riboflavin, when used as a supplement to diet #25, results in practically normal sebaceous glands but growth is still quite subnormal.

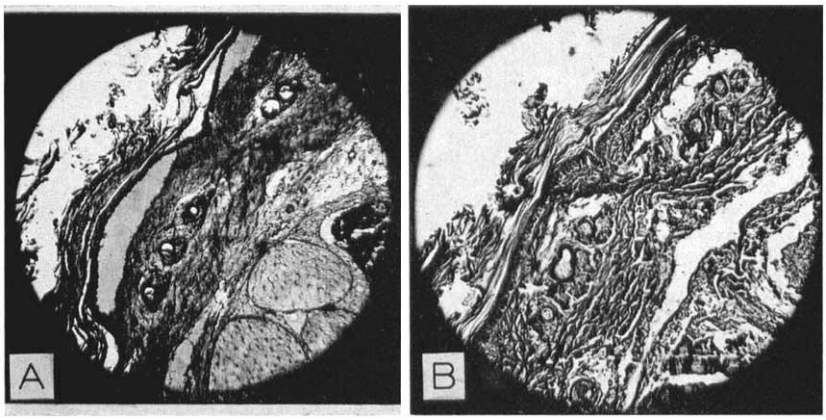

FIG. 1. Photomicrograph of cross section of rat tail

A. Section taken after rat had been depleted on a diet deficient in all the factors of the vitamin B-complex, except riboflavin and vitamin B_1. Note the partial atrophy of the sebaceous glands and the edema beneath the epithelial layer. H and E × 110.

B. Section of same rat taken after the administration of synthetic vitamin B_6 (100 micrograms per day) for 9 days. The sebaceous glands have increased and the edema has disappeared. H and E × 110.

STATISTICAL STUDY OF CASES

In a study of the effect of sunlight on the clinical manifestations of pellagra in 1937, Smith and Ruffin (10) pointed out that the typical sebaceous gland syndrome described above is one of four distinct types of dermatitis found in pellagra and one of the three types which is not directly precipitated by exposure to sunlight or other sources of radiant energy. Between July 1, 1930 and December 30, 1939, 512 pellagrins were studied at the Duke Hospital. "Dyssebacia" was observed in 61 patients or 12 per cent of the total.

[2] The supply of vitamin B_6, riboflavin, and thiamin chloride used in these experiments was kindly supplied by Merck & Company, Rahway, N. J.

Age. There is some indication that the prevalence of "dyssebacia" increases with the age of the patient (table 2). There were 4 cases in 60 pellagrins (7 per cent) under 21 years, 28 cases in 335 pellagrins (8 per cent) from 21 to 50 years, and 19 cases in 117 pellagrins (16 per cent) over 50 years of age.

Race and Sex. There were 434 white and 78 negro patients in this series. "Dyssebacia" was found in 46 of the white patients (10 per cent) and 15 of the negro patients (19 per cent). The prevalence of this syndrome is influenced more by sex than

TABLE 2

Incidence of "dyssebacia" in relation to age

	AGES (YEARS)						
	0–11	11–20	21–30	31–40	41–50	51–60	Over 60
Number of pellagrins	26	34	110	124	101	66	51
Number with "dyssebacia"	1	3	15	14	9	14	5
Percentage with "dyssebacia"	4	9	14	11	9	21	10

TABLE 3

Incidence of "dyssebacia" in relation to race and sex

	WHITE		COLORED	
	Female	Male	Female	Male
Number of pellagrins	284	150	57	21
Number with "dyssebacia"	16	30	8	7
Percentage with "dyssebacia"	6	20	14	33

race. Twenty-four cases were found in 341 females (7 per cent) and 37 cases in 171 males (22 per cent). The clearest picture is obtained when patients are grouped according to race and sex as shown in table 3 where "dyssebacia" was found in 6 per cent of white females, 14 per cent of colored females, 20 per cent of white males, and 33 per cent of colored males.

Season of the year. Pellagra occurs throughout the year but is more prevalent in the spring and early summer. In this series of 512 cases more than one-half were seen in May, June, and July. "Dyssebacia" occurs in association with pellagra throughout the year but in a slightly higher percentage in the colder

months. Among the 297 pellagrins studied in May, June, and July "dyssebacia" was seen in 23, or 8 per cent, of the cases. During the remaining 9 months of the year among 214 pellagrins 28, or 13 per cent, of the cases were recognized as having the syndrome.

Other factors influencing the prevalence of "dyssebacia." Only 61 cases of "dyssebacia" (12 per cent) were found in 512 cases

TABLE 4

Incidence of "dyssebacia" in relation to season of the year

	MONTH											
	January	February	March	April	May	June	July	August	September	October	November	December
Number of pellagrins...	15	13	18	35	116	104	77	27	30	31	24	21
Number with "dyssebacia".....	2	3	5	7	17	9	7	1	1	3	3	4
Percentage with "dyssebacia".....	13	23	28	20	15	9	9	4	3	9	13	19

TABLE 5

Incidence of "dyssebacia" in relation to other complications

	COMPLICATION				
	Psychoses	Peripheral neuritis	Alcoholics	Alcoholic psychoses	Deaths
Number of pellagrins.....	38	14	27	8	17
Number with "dyssebacia"....	11	5	11	6	5
Percentage with "dyssebacia".	29	36	41	75	30

of pellagra. The true incidence of the condition is certainly much higher than indicated by these figures. The incidence in our series has risen steadily since the hospital staff began to make a routine inspection of the face for this type of dermatitis. In the first six and one-half years of the study, 15 cases were found in 309 pellagrins (5 per cent) while 46 cases were detected in 203 pellagrins (22.6 per cent) studied during the last 3 years.

The incidence of this dermatitis was higher in the 234 patients who were hospitalized (20 per cent) than in the 278 who were

studied in the out patient department (6 per cent). As a rule the more acute pellagrous cases were hospitalized and had the advantage of being examined by three or more members of the hospital staff. In the 94 pellagrins studied in the hospital during the last 3 years, 32 cases involving the characteristic sebaceous gland changes (35 per cent) were detected.

"Dyssebacia" was present in 5 of the 17 patients who died of pellagra or pellagra and associated infections. Eleven of the 38 cases with the psychoses of pellagra also had this complication. The highest incidence of this syndrome is found in the group of alcoholic pellagrins. In this series 11 of the 27 alcoholic pellagrins had the syndrome and it was found in 6 of the 8 alcoholic patients (75 per cent) who had psychoses. The increased excessive use of alcohol probably explains in part the higher incidence of this lesion in males and the frequency of this complication in negro males (table 5).

TREATMENT

When the pellagrin is treated with a general well-rounded diet, including all the members of the B-complex, the "dyssebacia" improves simultaneously with the other lesions attributable to deficiency of the factors of this complex and is cured in about the same length of time. Treatment with autoclaved yeast and crude liver extract results in rapid and complete healing of the lesions of "dyssebacia." Liver extracts, purified for the purpose of concentrating the pernicious anemia factor, have no curative value. Nicotinic acid usually cures "dyssebacia" but more slowly than yeast and crude extracts of liver, and healing occurs only after the acute symptoms of pellagra have disappeared and the appetite has returned. This suggests that nicotinic acid probably acts indirectly by curing the pellagra and stimulating the appetite and is not the specific etiologic factor.

A small series of cases have been treated under controlled conditions where the patient was subsisting upon a standard diet which is deficient in nicotinic acid and partially deficient in other members of the vitamin B_2-complex. This diet, which was introduced by Ruffin and Smith (34) and called the Standard

TABLE 6

PATIENT	ADMISSION DATE	RACE	SEX	AGE	TREATMENT	DAYS OF TREATMENT	EFFECT ON "DYSSEBACIA"	REMARKS	DIET
R. L. B.	7/27/36	W	M	35	P. L. E. (L)	6	None		Basic #1
A. M. C.	5/11/37	W	F	51	P. L. E. (L)	18	None	Later cured with C. L. E.	Basic #1
E. L.	11/16/32	C	M	47	C. L. E. (V)	6	Plugs fell out in 5 days, oily secretion in 6 days		Basic #1
B. B.	11/26/35	W	M	45	C. L. E. (V)	7	Cured in 7 days		Basic #1
M. J.	5/25/36	C	F	29	C. L. E. (V)	6	Marked improvement in 4 days		Basic #1
H. L. B.	7/27/36	W	M	35	C. L. E. (L)	6	Cured in 6 days		Basic #1
A. N. C.	5/11/37	W	F	51	C. L. E. (L)	6	Plugs fell out in 4 days; cured in 6 days		Basic #1
E. E.	5/19/38	W	F	66	Yeast, B.		Cured		Home diet
S. R. S.	1/30/39	C	M	65	Yeast, B. A.		Plugs fell out in 2 days; cured in 4 days	The lesion grew worse while patient received N. A.	Basic #1
M. J.	5/25/36	C	F	29	Riboflavin	5	None	Cured later with C. L. E	Basic #1
J. W.	4/ 4/39	W	M	47	Riboflavin	5	None	Cured later with N. A.	Basic #1
L. M. D.	5/15/39	W	M	63	Riboflavin	5	Slow improvement	Cured later with N. A.	Basic #1
A. S.	5/22/39	W	M	68	Riboflavin	5	Slow improvement in 2 days, then stationary	Cured later with N. A.	Basic #1
T. V. C.	7/10/39	W	M	32	Riboflavin	5	None	Cured later with coramine	Basic #1
W. H. B.	10/26/37	W	M	42	Nicotinic acid	7	Marked improvement	No change during 7 day control period	Basic #1
J. M.	3/ 1/38	W	M	54	Nicotinic acid	9	Definite improvement	No change during 9 day control period	Basic #1
R. G. C.	4/ 5/38	W	M	41	Nicotinic acid	14	Cured in 14 days		Basic #1
C. W. J.	5/19/38	W	M	8	Nicotinic acid	7	Cured slowly		Basic #1
W. W.	5/24/38	C	M	24	Nicotinic acid	16	Marked improvement	No improvement with B_1, R.F., or C. L. O.	Basic #1
B. E. E.	6/ 2/38	W	F	40	Nicotinic acid	7	Cured	EKG reversed	Basic #1

B_1, thiamin chloride; R.F., riboflavin; N. A., nicotinic acid; C. L. O., cod liver oil; P. L. E., parenteral liver extract; C.L.E.. crude liver extract; Yeast, B., yeast, brewer's; Yeast, B.A., yeast, brewer's autoclaved. (L), Lederle (V) Valentine.

Basic Diet was a modification of the original one on which Goldberger produced pellagra in human volunteers. We have observed the development of "dyssebacia" in one patient while confined to bed and subsisting on the basic diet, and have noted a striking increase in the severity of the symptoms in a number of other patients under these controlled conditions. Spontaneous healing has not been observed.

CASE REPORTS

The following case reports give an example of our method of testing the therapeutic effect of certain vitamin factors on the lesion:

Case 1. A. M. C., a white female, aged 51 was admitted to the hospital May 11, 1937 with the typical dermatitis of pellagra on the dorsum of the hands, extensor surfaces of the arms, and on the exposed surfaces of the neck. Moderately severe "dyssebacia" was present with lesions about the alae nasi and over the nose.

The patient was confined to bed and fed the basic diet with the supplements which include iron, calcium, vitamin C and cod liver oil for a period of 12 days. There was some increase in the sebaceous gland lesions during this time. The basic diet was continued with the cod liver oil supplement and treatment was started with 1 cc. of Lederle's parenteral liver extract daily and continued for 18 days. There was a marked increase in the sebaceous gland lesions after 30 days treatment with cod liver oil and 18 days with parenteral liver.

The treatment described above was continued and supplemented by 20 cc. of a crude liver extract prepared for us by the Lederle Laboratories. Most of the pernicious anemia factor was removed from the preparation. There was dramatic improvement in the sebaceous gland lesion after 4 days. The face was oily and smooth and apparently normal by the 7th day of treatment.

Case 2. A. S., a white male aged 68 was admitted to the hospital May 22, 1939 with typical dermatitis of pellagra over the hands, excoriations about the perineum, a scrotal lesion and a severe psychosis. There was marked "dyssebacia" with lesions about the alae nasi and over the nose.

The patient was confined to bed and fed the basic diet without supplements. He received 40 mg. of riboflavin in 10 per cent urea solution daily for 6 days. Between 18 and 24 hours after the first injection of riboflavin there was an extrusion of a few of the sebaceous plugs. There was no further improvement during the next 5 days of flavin treatment.

Because of the severity of his disease he was changed to a well-balanced diet and given nicotinic acid and Valentine's liver extract. Improvement began in the sebaceous gland lesions in 4 days. There was marked improvement in 6 days and the face was apparently normal in 10 days.

Case 3. W. H. B., a white male aged 42 was admitted to the hospital October 26, 1937 with the typical dermatitis of pellagra over the hands and feet. He also had a psychosis and sebaceous gland lesions over nose, face and chin (11, plates).

The patient was confined to bed and given the basic diet without supplements for a period of 7 days. No improvement was noted in the sebaceous gland lesions during this period of observation. The anorexia and psychosis increased in severity.

The basic diet was continued and he was given 60 mg. of nicotinic acid daily for the next 10 days. The nicotinic acid was given by either the intravenous or intramuscular route for the first 7 days and orally thereafter. There was marked improvement in the psychosis and the general condition of the patient on the 3rd day of treatment. The sebaceous gland lesions began to improve on the 5th day and the face was practically normal by the 10th day (11).

Case 4. S. R. S., a negro male aged 65 was admitted to the hospital January 30, 1939 with mild subsiding pellagrous lesions on the hands and arms, a mild psychosis, and severe "dyssebacia" with lesions about the alae nasi, over the nose and a mild lesion on the forehead. The sebaceous follicles were filled with innumerable plugs of hardened sebum which projected above the surface of the skin. When viewed with a hand lens they appeared as tiny circular discs of grayish waxy material which usually projected above the surface, but occasionally some were broken off or worn down and were visible at the surface, or even below the surface, of the surrounding skin. The plugs were firmly anchored in the sebaceous follicles and the entire face appeared immobile and rigid (fig. 2a).

The patient was confined to bed and fed the basic diet without supplement of vitamins or minerals and observed for 10 days. No gross change occurred in the sebaceous glands during this period of observation. A biopsy specimen of the skin was taken from the right side of the face near the alae nasi February 9, 1939 (fig. 2c, e). Reversed ocular examination of the microscopic section from this specimen (magnification × 10) showed marked hyperplasia of the sebaceous glands throughout the corium. Low power examination with magnification of 100, revealed an epidermis of normal thickness with some flattening of the papillary pegs and a moderate hyperkeratosis. There was no acanthosis and the epidermal cells appeared normal. There was, however, marked follicular dilatation, the follicles being plugged with dry sebaceous material. There was little round cell infiltration in the subepidermal layer and almost no round cell infiltration surrounding the hypertrophied sebaceous glands. Certainly any cellular response was minimal. There was moderate edema of the cells lining the sebaceous glands and some edema in the surrounding tissue. The sweat glands and appendages appeared normal.

During the next 10 days the patient received 3,750 mg. of nicotinic acid. No evidence of improvement was noted in the sebaceous gland lesions during this period of treatment.

On February 20, he received 750 mg. of nicotinic acid and 15 gm. of autoclaved yeast. The next day the nicotinic acid was repeated and the autoclaved yeast increased to 45 gm. By 2:30 on February 22 there was an amazing improvement in the face. Most of the sebaceous plugs had been extruded leaving large crater-like openings (fig. 2b). By February 23 all of the plugs had disappeared and the skin was soft and pliable and covered with an oily secretion. A second biopsy specimen was taken from the left side of the face near the alae nasi on March 22 (fig. 2d, f). Sections from this specimen revealed loss of edema of the cells lining and surrounding the sebaceous glands and the cells themselves had assumed a

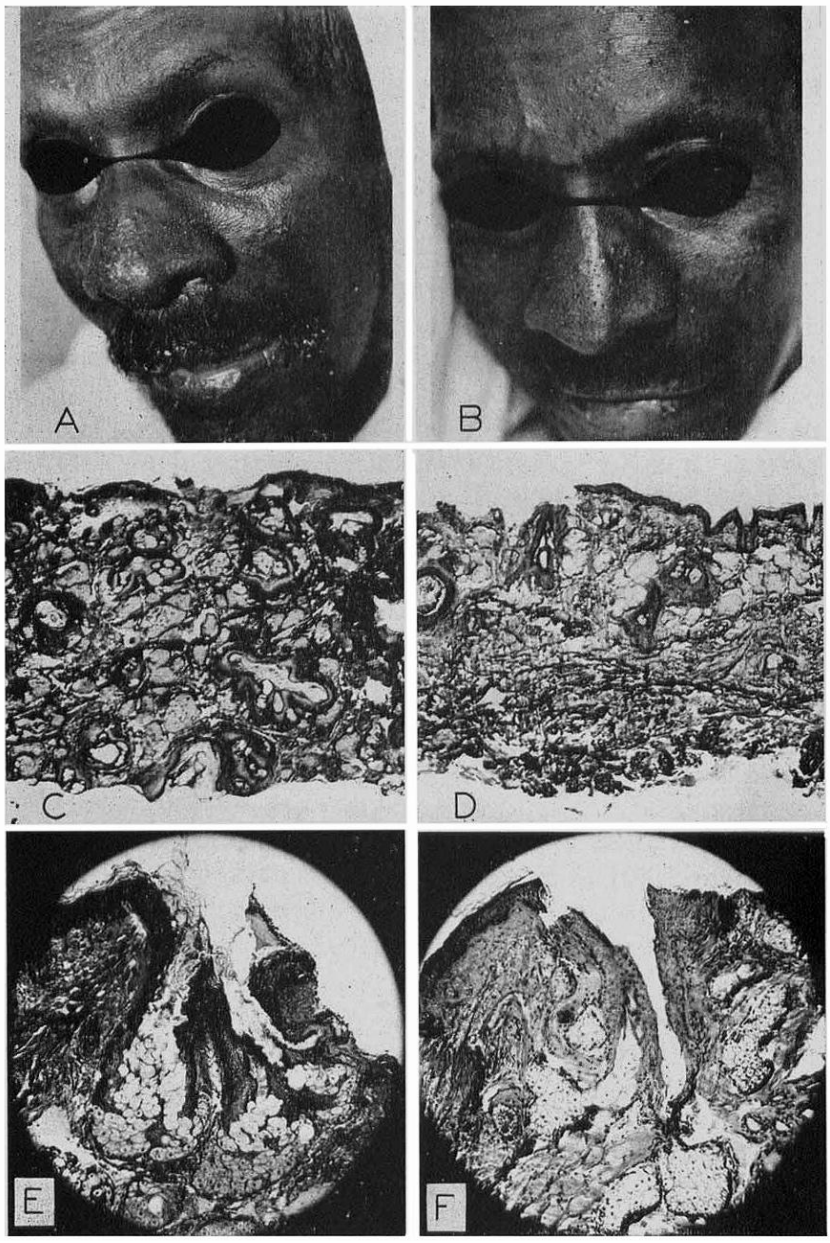

FIG. 2. A. Gross appearance of lesions in patient with "dyssebacia."

B. The same patient 48 hours after treatment with autoclaved yeast.

C. Photomicrograph of skin of alae nasi of this patient before treatment. Note the apparent hypertrophy of the sebaceous glands and the plugs of inspissated sebum in the ducts. Masson. × 35.

D. Photomicrograph of same patient after 40 days of yeast treatment. The sebaceous glands have apparently returned to normal and the ducts are clear. Masson. × 10.

E. Photomicrograph showing higher power of C. H and E × 100.

F. Photomicrograph showing higher power of D. H and E × 100.

more normal appearance. Hyperplasia of the sebaceous glands and plugging of the follicles had disappeared and all the tissues showed reorganization and improved architecture.

DISCUSSION

There are in the human being, apparently, two distinct types of sebaceous gland dysfunction associated with vitamin deficiency. One is related to vitamin A deficiency, the other to vitamin G-complex deficiency. It is with the latter type, which for convenience we have termed "dyssebacia," that we are particularly concerned in this paper. However, on account of their similarity and prevalence on mixed vitamin deficiencies, a discussion of both seems necessary. The lesion associated with vitamin A deficiency has been recognized as a clinical entity and termed phrynoderma or toadskin. The sites involved are the flexor surfaces of the arms and legs, not the areas where sebaceous glands are most numerous. A condition which is clinically indistinguishable from phrynoderma is keratosis pilaris. The description of the lesion is much the same, namely, "a follicular affection in which horny accretions of about pinhead size give the skin a stippled appearance resembling goose flesh . . . keratosis pilaris has a predilection for the extensor surfaces of the arms and thighs" (31). However, we are inclined to agree with Lehman and Rapaport (28) that keratosis pilaris, and its synonyms, lichen pilaris, pityriasis pilaris, lichen spinulosum, ichthyosis follicularis, etc., are merely descriptive terms for the cutaneous manifestations of phrynoderma. The basis for considering these lesions the result of avitaminosis A is that they are usually associated with other symptoms of A deficiency, as xerophthalmia, night blindness, etc. The histology of the skin is that found in A deficiency (28), the lesions respond slowly (2–4 months) to treatment with vitamin A, while the classical A deficient lesions heal rapidly.[3] These sebaceous gland lesions

[3] Since this manuscript went to press Crandon, Lund and Dill (New Eng. J. Med., **223**, 353 (1940) reported the experimental production of a syndrome indistinguishable clinically from phrynoderma in a man on a vitamin C deficient diet. The lesions yielded rapidly to vitamin C treatment. The last case of phrynoderma observed by us had a normal level of vitamin A and a low level of vitamin C in the blood serum. The condition yielded to treatment with vitamin C in addition to the vitamin B-complex. No vitamin A was given.

do not respond to yeast extract (32). On the contrary, the syndrome "dyssebacia," described in detail above and found associated with pellagra, does not respond to vitamin A and does respond to yeast and liver, both excellent sources of the B-complex. It may be argued that liver contains vitamin A as well as vitamin B-complex. That is true but the yeast used in these tests, giving equally good results, was assayed on rats and failed to protect against xerophthalmia, even when fed at a level of 10 per cent. When sources of the B or G-complex are used, the "dyssebacia" clears up as rapidly as the typical pellagra lesions. But the synthetic factors of the B-complex tried thus far have not been quite so satisfactory. In our hands thiamin chloride and riboflavin have had little, if any, effect. At least they have no specific effect. Nicotinic acid, on the other hand, was curative in most cases but the response of the "dyssebacia" was more gradual than that of the typical pellagra lesions. It must be remembered also that since these patients were pellagrins they were presumably suffering from a primary deficiency of nicotinic acid. The correction of this deficiency would probably correct the effect of any secondary deficiency which might be responsible for the lesions in question (33). Other more recently synthesized members of the G-complex must be tested before we can be sure of the specific factor involved, but since we were able to get a dramatic response with yeast which had been autoclaved for $2\frac{1}{2}$ hours at 15 pounds pressure, it is logical to assume that the factor is contained in the heat stable portion of the vitamin B-complex.

Etiologically, the lesions of "dyssebacia" appear to be quite like the lesions produced in the rat, although histologically they appear quite different, the rat lesion being characterized by atrophy while in the human there appears to be hypertrophy and hyperplasia.

We would like to offer the following as a possible differentiation of the two similar appearing sebaceous gland lesions in the human being, phrynoderma, associated with a vitamin A deficiency, and "dyssebacia," with a G-complex deficiency. In the first case the sebaceous gland lesions are secondary to the plugging of the sebaceous follicles by products of the keratinization which takes

place as a result of vitamin A deficiency. In the second case the change in the sebaceous glands is primary and due specifically to a lack of one or more of the vitamin G-complex factors. It will be noted that in the case of this lesion the site follows the distribution of the sebaceous glands, appearing first in the alae nasi and about the nose where the glands are most numerous, whereas in the case of the former, this is not true.

SUMMARY AND CONCLUSIONS

1. Experimental sebaceous gland lesions have been produced in the tails of rats on vitamin G-complex deficient diets and the curative factors studied.

2. The experimental lesions were not cured by nicotinic acid, adenylic acid (muscle), riboflavin, vitamin B_6, vitamin B_1, or parenteral liver extract when fed singly to rats on a diet deficient in all the factors of the vitamin G-complex. However, when the lesions developed in rats on the flavin deficient diet of Bourquin and Sherman, riboflavin alone affected a cure.

3. Crude aqueous extract of liver or autoclaved yeast consistently prevents or cures the experimental lesion. A combination of riboflavin and vitamin B_6 as a supplement to the completely G-complex deficient diet results in practically normal sebaceous glands, but growth remains subnormal.

4. A sebaceous gland syndrome frequently found associated with pellagra has been described and termed "dyssebacia." The lesions, occurring chiefly on the face, are characterized by dryness of the skin and the presence of plugs of inspissated sebum projecting from the sebaceous follicles, thus giving a sandpaper appearance.

5. In a statistical study of 512 pellagrins, "dyssebacia" was observed more frequently in adults than in children and in males than in females. The incidence is highest in negro males, particularly alcoholics with dementia.

6. The outstanding histological change is hyperplasia of the sebaceous glands, the follicles being dilated and plugged with dry sebaceous material.

7. "Dyssebacia" is readily cured by autoclaved yeast or crude

extracts of liver. On the other hand, vitamin B_1 and parenteral liver extract are ineffective. Synthetic riboflavin has little effect in the active pellagrin who has not been treated with nicotinic acid. The latter is curative in most instances but is not as effective as yeast or crude extracts of liver.

8. "Dyssebacia" results from a deficiency of some factor or combination of factors present in the vitamin G-complex.

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DISCUSSION

DR. HAMILTON MONTGOMERY, *Rochester, Minnesota:* I was very much interested in the histologic studies as given in this paper. One of the fellows at The Mayo Clinic voluntarily went on a rigid vitamin A deficient diet for six months. At the end of that time he was disappointed because he had failed to develop symptoms of night blindness. Clinically one could see no change in the texture of his skin, even with a magnifying glass. Histologic study of a specimen removed from the skin of the forearm revealed relative and absolute hyperkeratosis, follicular plugging and a peculiar vacuolization of some of the prickle cells, homogenization of the connective tissue fibers in the cutis and atrophy of the dermal appendages including the sweat glands.

Two weeks after this fellow had returned to a normal diet with the addition of vitamin A, another specimen for biopsy was taken two inches away from the

first site for biopsy. It was found histologically that the skin had practically returned to normal, there still being mild follicular hyperkeratosis.

DR. D. M. WOOLEY, *New York:* I would like to ask if Doctor Smith has made any observations, particularly biopsies, on eroded noses and tails which develop in animals kept on synthetic diets particularly those deficient in Vitamin B_1 and riboflavin, and also whether he has had an opportunity to test against these lesions.

DR. PAUL GROSS, *New York City:* For the past few years, I have been interested in the treatment of certain skin eruptions with vitamin B complex. It is my impression that the excellent results obtained in selected cases, by injection of liver extract, so far could not be duplicated with individual administration of riboflavin and nicotinic acid. As Dr. Smith has shown, clinical as well as in the animal experiment, a combination of several vitamins of the B complex is necessary to clear up certain lesions which would confirm our experience in dermatologic conditions. As far as the lesions on the tail of rats are concerned, we find a diffuse scaling associated with the filtrate fraction deficiency, while the severe necrotic lesions of the tail are the results of vitamin B_6 deficiency.

DR. J. LAMAR CALLAWAY, *Durham, N. C.:* I had an opportunity to see the histological sections of lesions taken from the nose in several patients. In each case there was a tremendous amount of hyperplasia observed before treatment with the Vitamin B complexes. The epidermis was perfectly normal except for plugging and the dermis showed hyperplasia of the sebaceous glands with considerable edema and a moderate amount of round cell infiltration surrounding these sebaceous glands. The clinical response in most every case was rapid and biopsy specimens taken from the opposite side of the nose after a few days of treatment showed the sebaceous glands to have returned essentially to normal. In the experimental studies there was considerable atrophy of the sebaceous glands in the tail of the rat, whereas in the human the biopsies that we studied all showed tremendous hyperplasia rather than atrophy of the sebaceous glands.

DR. DAVID T. SMITH, *Durham, N. C.:* We had recently, in our medical clinic, a patient with marked phrynoderma which has been attributed to a deficiency of vitamin A. A biopsy showed plugs of inspissated sebum in the orifices of the sebaceous glands and atrophy of the glands. There was no involvement of the sebaceous glands of the nose or face in this case.

In patients with pellagra and sebaceous gland dysfunction the lesions are usually confined to the face and the extremities are not involved. The sebaceous gland lesions are not inflammatory, there is no discharge, and they would not be confused with acne.

SUSAN GOWER SMITH, *Durham, N. C.:* No sections were prepared from the nose of the experimental rats. We have made and studied tail sections of rats on vitamin A deficient diets and on B deficient diets. Both show similar though less marked pathology than the vitamin G deficient rats. The sebaceous glands are practically normal on a vitamin A deficient diet if the level of vitamin G is maintained by feeding the autoclaved yeast separately. This test was not pos-

sible in the case of rats on a vitamin B deficient diet due to the marked anorexia and refusal to consume the yeast. On the contrary, maintaining the level of vitamin B or vitamin A in rats on a vitamin G deficient diet has no effect on the lesion.

We do not assume that the rat lesion observed in these experiments is the same as the one observed in patients with pellagra. Both, however, involve the sebaceous glands and both are controlled by the same factor or group of factors.

As yet neither synthetic vitamin B_6 nor synthetic pantothenic acid has been tried on the lesion in pellagrins but plans have been formulated for this.